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Endometriosis and genetic factors involved

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Abstract

Endometriosis is a common estrogen-dependent inflammatory disorder, which is marked by the growth of endometrial tissue outside the uterus, causing severe symptoms and diagnostic challenges. This article examines the symptoms, such as pelvic pain and infertility, and discusses the diagnostic methods including transvaginal ultrasonography and magnetic resonance imaging (MRI). The significant impact on quality of life and the various medical and surgical treatments available are explored. Additionally, this composition addresses the fertility issues associated with endometriosis and the factors contributing to its development, including genetic predisposition and environmental influences. Current research efforts aimed at improving diagnostics and treatments are also reviewed, highlighting the potential for better management and future cures.

Keywords: Endometriosis; Infertility; Uterus; Genetics

1. Introduction

Endometriosis is a painful gynecological condition characterized by the presence of endometrial tissues outside the uterine cavity [1]. The women with the condition often suffer from dysmenorrhea, dyspareunia, infertility, and pelvic pain, which negatively impact patients' quality of life. Endometriosis is a benign disease. However, its biological characteristics are similar to tumors with progressive and invasive growth, recurrence, and a tendency to metastases [2].

This disease is diagnosed in approximately 10% of women of reproductive age, with its prevalence increasing to 50% in infertile women. It is more common in women of Philippine, Indian, Japanese, and Korean origin. Despite the high prevalence of the disease, the diagnosis of endometriosis is often delayed by 7–10 years due to the complexity of its pathogenesis. Laparoscopy is currently established as the gold standard for the definitive identification of endometriosis, with histological biopsy confirming the diagnosis [3].

Many women gain only limited benefit from current treatments for endometriosis. Numerous patients experience unacceptable systemic adverse effects. Consequently, research for the development of efficient treatments for endometriosis that also would prevent infertility is ongoing [1].

Mechanisms involved in this complex and multifactorial disease include estrogen dependence, aberrant inflammatory response, angiogenesis abnormalities, genetic factors, and epigenetic alterations [4]. Genetic studies on endometriosis initially did not succeed. However, recent advancements in technology have led to a deeper comprehension of the genetic factors contributing to endometriosis. Candidate gene investigations, gene association studies, and genome-

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wide association studies (GWAS) have identified more than 30 potential genes. Nevertheless, research assessing the significance of these genes in understanding endometriosis's pathogenesis is ongoing [3].

2. Symptoms and Diagnosis of Endometriosis

Endometriosis is a complex gynecological disease and it is known for being an inflammatory process that can lead to painful and uncomfortable symptoms, to this day the exact cause is unknown and it remains theoretical [5]. But as we said it is believed to result from a combination of genetic, hormonal, and environmental factors.

In the patients who suffer from this condition the two major clinical symptoms are chronic pelvic pain and infertility [6], some other reported symptoms are painful periods, dysmenorrhea, dyspareunia, pain on defecation and dysuria [7,8]. With that in mind, we can say that endometriosis cannot only affect the reproductive organs but also can involve some affections on the bladder, bowel, nerves, urine organs, pleura, diaphragm, lungs, and brain [7].

The diagnosis of this gynecological condition may not always be evident, despite the presence of symptoms. Considering all the symptoms, it can be determined that it fits the criteria for being classified as a syndrome [7]. This diagnosis relies entirely on clinical experience, which considers age, symptoms, clinical examination, imaging, and identification [9]. We only can get a very specific diagnosis when the patient has symptoms and visible lesions. When there is suspicion of endometriosis, the diagnosis can be verified with the use of laparoscopy [9]. During this surgical procedure, key elements such as endometrial stromal cells, endometrial epithelial cells, and indications of chronic bleeding can be identified [6]. Other non-surgical diagnostics like imaging [9] such as transvaginal ultrasonography [8] are important before the surgery.

3. The influence of Endometriosis on the Quality of Life

Endometriosis symptoms frequently hinder women's social, professional, academic, and economic capabilities [6]. This can lead to changing the quality of life of these patients, not only directly in some physical way causing other effects some of which are correlated with psychological consequences like depression or anxiety [10], Additionally, women with endometriosis may experience reduced sexual satisfaction as a result of dyspareunia, or painful intercourse. This severe pain causes 50% of women with this condition to spend entire days in bed, with an average of 17.8 days per day [11], affecting patients on an individual level, and diminishing the quality of life for the patients.

Symptoms of endometriosis have the potential to alter the trajectory of an individual's life from their teenage years and may continue until menopause, as those affected may suffer from chronic pain throughout that period [7].

4. Medical and Surgical Treatment of Endometriosis

Choosing the treatment is important taking into account the age, extent and stage of the disease, and the presence of gastrointestinal or urinary symptoms [12].

One of the hormonal treatments focuses on reducing estrogen levels and decreasing inflammation. The contraceptive pill is commonly used as first-line treatment for pelvic pain [12].

Gonadotropin-releasing hormone (GnRH) agonists are considered as second-line treatments to reduce estrogen levels in the body; however, ovulation may occur during treatment. Nevertheless, this treatment can generate menopause-like effects. To counteract these effects, low-dose estrogen replacement therapy can be added [12].

In recent research, it has been found that Elagolix, an oral GnRH antagonist, is effective in relieving dysmenorrhea and pelvic pain associated with endometriosis when administered in high doses, either twice daily or daily [7].

For surgical treatment, in women aged between 30 and 40 years, hysterectomy has been employed as a surgical option to alleviate pain associated with endometriosis in most cases [13].

5. Endometriosis and Infertility

Infertility emerges as a major clinical concern in the context of endometriosis, significantly impacting the quality of life of around 50% of affected women [13].

Inflammation, as a central process in endometriosis, triggers pain, adhesion formation, and consequently infertility [12].

Managing infertility in women with endometriosis poses challenges within the medical field. Previously, laparoscopic surgery was common to treat all stages of endometriosis, but now doctors prefer to avoid such intervention in ovarian endometriomas until after completing fertility treatments [7].

In the treatment of infertility associated with endometriosis, in vitro fertilization (IVF) has increasingly been preferred because ovulation induction combined with intrauterine insemination may increase the risk of recurrent pain or disease progression [7].

It has been observed that ovarian endometriotic cysts are commonly associated with infertility and carry a higher risk of developing ovarian cancer associated with endometriosis [6].

6. Causes and risk factors of endometriosis

Endometriosis, being a multifactorial etiology, does not have only a defined cause, rather it is the result of the combination of irregularities in the hormonal, immunological, ethnic, genetic and environmental systems; On the other hand, it has been proven among various clinical trials that estrogen is the main biological driver of the inflammatory response in this condition [7].

In addition to the possible causes already mentioned, there are elements that contribute greatly to the evolution of the disease, such as age, sex, diet, microorganisms, toxins, stress, anxiety, medication side effects or surgeries of the female reproductive system [14].

On the other hand, we have the risk factors that harbor some relationship with endometriosis, such as the arrival of early menarche, short duration of the menstrual cycle, a low body mass index and retrograde; But each of these must be inspected very carefully, reflecting on whether they are causal or part of the pathological process of the same ailment, depending on the individual [12,15].

From a nutritional point of view, it has been proven that the relationship between high intake of dairy products decreases the risk of endometriosis, but on the other hand, a prolonged consumption of red meat, trans fats and saturated fats increases the threat of the disease [16].

7. The Role of Genetics in Endometriosis

In most investigations of diseases to which a definitive cause has not yet been assigned, an indispensable step for the resolution of the mystery is the review at a molecular and genetic level of the disease, with the identification of the genes involved and the function that could be altered (Table 1) [22].

Table 1 Characteristics of the genes most important in the development of endometriosis (22)

Name of gen	Location	Encoding	Involvement
IL1A rs6542095	2.3 kb downstream of IL1A	IL-1α, a member of the interleukin-1 cytokine family	The regulation of the proinflammatory cytokines and chemokines production
NFE2L3 rs12700667 and rs7798431	290 kb and 331 kb downstream, respectively, of NFE2L3 gene	A member of the cap 'n' collar basic-region leucine zipper	Regulator of cell differentiation, inflammation and carcinogenesis
GREB1 rs13394619	Between exons 9 and 10 of GREB1 gene		Estrogen dependent growth of endometriosis
FN1 rs1250248	Between exons 10 and 11 of FN1	Fibronectin	In cell migration and adhesion processes in the blood coagulation, wound healing, embryogenesis and metastasis

WNT4 rs7521902	21 kb upstream of WNT4	Proteins	Oncogenesis and different embryo developmental processes
CDKN2B-AS1 rs1537377	48 kb upstream of CDKN2B-AS1		upregulated in ovarian cancer cell lines
ID4 rs7739264	52 kb upstream of ID4	Protein from the inhibitor of DNA binding (ID) family	Initiation, maintenance and cancer progression, besides the drug resistance
RND3 rs6734792	280 kb upstream of RND3 gene	GTPase protein superfamily	Modulator in migration and proliferation of tumor
VEZT rs10859871	17 kb upstream of VEZT	Transmembrane protein localized in adherens junctions that binds to myosin VIIA	Target for development of endometriosis
ETAA1 rs4141819	227 kb upstream of ETAA1	Repair protein, recruited to stalled forks by RPA	Undetermined

Endometriosis is a chronic inflammatory disorder, with a notable imbalance of the body at the immune level, with an increased release of growth factors, cytokines and chemokines, but an unbalanced range of neutrophils, natural killers (NK), T helpers and B; causing a greater tissue response, continuing the manifestation of inflammation in a vicious cycle [17].

There are so far a large number of genes identified that are related to endometriosis, among these it is important to highlight HOXA10 that is involved in the development of pinopods in the luteal phase of the endometrium, causing an irregular menstrual cycle with a high probability of ending with several reproductive disorders [18] .

In the genetic field, it is vital to point out the diseases related to endometriosis due to their similarities in causes, pathology or interposed genes, such as irritable bowel syndrome, ankylosing spondylitis, heart disease, allergies, infertility, fibromyalgia, fatigue and cancer [22].

8. Research and advances in endometriosis

Over the years, treatments for endometriosis have been targets of little scientific research, this is because the treatment alternatives for this disease are still limited and the cure rate is not sufficient, the search for ways to treat the symptoms and modifying the course of the disease is of utmost importance to improve the quality of life of patients with endometriosis, which is why studies have been carried out in literature, which show that there is an influence on the diet and foods consumed. in endometriosis with a hormonal modification altering the inflammatory or oxidative response [19].

On the other hand, a “representative microengineered vascularized endometrium on a chip has been constructed to closely recapitulate the endometrial microenvironment consisting of three distinct layers including epithelial cells, stromal fibroblasts, and endothelial cells in a 3D extracellular matrix in a spatiotemporal manner”[20].

9. Emerging technologies

Currently there are new technologies for the study of endometriosis, one of them consists of a recent lineage tracing and tissue cleaning microscopy, thus reconstructing a sophisticated 3D model, which offers us a new perspective on the understanding of endometriosis and the endometrial glandular structure, in particular the interconnection of the basal glands. Similarly, we can find new sequencing technologies, particularly whole-genome DNA sequencing, which are showing us mutations at the somatic level, that even these genes drive cancer in a normative and eutopic endometrium of patients. On the other hand, single-cell RNA sequencing shows us the transcriptome of individual endometrial cells, which illuminates new fields for understanding the diversity and variety of cellular subpopulations of the types of cells that we can find in the endometrium and certainly in endometriotic lesions. Likewise, new cultures of endometrial epithelial organoids have been implemented, which help us replicate the glandular epithelium; these are providing us with manageable models to study endometriosis. Moreover, methylome sequencing is used as a complement; this

technique provides us with information about the regulation of genes, as well as the influence of environmental factors, which are extremely important to take into account for a better understanding of this disease [21].

10. Conclusion

Endometriosis is a disease that affects millions of women around the world, therefore is important an early diagnosis, in order to prevent many of the complications that may arise. Likewise, it is of interest to understand its history, genetics, which leads us to a deeper understanding of the aggravations that people with a uterus may present, since as is well known, endometriosis is a factor in infertility, and one of the most common, prolonged pelvic pain that interferes with social and work activities.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Esfandiari F, Favaedi R, Heidari-Khoei H, Chitsazian F, Yari S, Piryaei A, et al. Insight into epigenetics of human endometriosis organoids: DNA methylation analysis of HOX genes and their cofactors. Fertility and Sterility [Internet]. 2021 Jan 1;115(1):125–37. Available from: https://doi.org/10.1016/j.fertnstert.2020.08.1398

[2] Geng R, Huang X, Li L, Guo X, Wang Q, Zheng Y, et al. Gene expression analysis in endometriosis: Immunopathology insights, transcription factors and therapeutic targets. Frontiers in Immunology [Internet]. 2022 Nov 30;13. Available from: https://doi.org/10.3389/fimmu.2022.1037504

[3] Zubrzycka A, Zubrzycki M, Perdas E, Zubrzycka M. Genetic, epigenetic, and steroidogenic modulation mechanisms in endometriosis. Journal of Clinical Medicine [Internet]. 2020 May 2;9(5):1309. Available from: https://doi.org/10.3390/jcm9051309

[4] Chen H, Malentacchi F, Fambrini M, Harrath AH, Huang H, Petraglia F. Epigenetics of estrogen and progesterone receptors in endometriosis. Reproductive Sciences [Internet]. 2020 Jul 22;27(11):1967–74. Available from: https://doi.org/10.1007/s43032-020-00226-2

[5] Antonio Simone Laganà, Garzon S, Götte M, Viganò P, Franchi M, Ghezzi F, et al. The Pathogenesis of Endometriosis: Molecular and Cell Biology Insights. International journal of molecular sciences [Internet]. 2019 Nov 10 [cited 2024 May 31];20(22):5615–5. Available from: https://www.mdpi.com/1422-0067/20/22/5615

[6] Wang Y, Nicholes K, Shih IM. The Origin and Pathogenesis of Endometriosis. Annual review of pathology [Internet]. 2020 Jan 24 [cited 2024 May 31];15(1):71–95. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7980953/

[7] Bulun SE, Yilmaz BD, Sison C, Miyazaki K, Bernardi L, Liu S, et al. Endometriosis. Endocrine reviews [Internet]. 2019 Apr 17 [cited 2024 May 31];40(4):1048–79. Available from: https://academic.oup.com/edrv/article/40/4/1048/5469279

[8] Philippa T.K. Saunders, Horne AW. Endometriosis: Etiology, pathobiology, and therapeutic prospects. Cell [Internet]. 2021 May 1 [cited 2024 May 31];184(11):2807–24. Available from: https://www.cell.com/cell/fulltext/S0092-8674(21)00576-6?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867421005766%3Fshowall%3Dtrue

[9] Koninckx PR, Fernandes R, Ussia A, Schindler L, Arnaud Wattiez, Shaima Al-Suwaidi, et al. Pathogenesis Based Diagnosis and Treatment of Endometriosis. Frontiers in endocrinology [Internet]. 2021 Nov 25 [cited 2024 May 31];12. Available from: https://www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2021.745548/full

[10] Luigi Della Corte, Claudia Di Filippo, Gabrielli O, Reppuccia S, Lucia V, Ragusa R, et al. The Burden of Endometriosis on Women's Lifespan: A Narrative Overview on Quality of Life and Psychosocial Wellbeing. International journal of environmental research and public health/International journal of environmental

research and public health [Internet]. 2020 Jun 29 [cited 2024 May 31];17(13):4683–3. Available from: https://www.mdpi.com/1660-4601/17/13/4683

[11] Missmer SA, Tu FF, Agarwal SK, Chapron C, Soliman AM, Chiuve S, et al. Impact of Endometriosis on Life-Course Potential: A Narrative Review. International journal of general medicine [Internet]. 2021 Jan 1 [cited 2024 May 31];Volume 14:9–25. Available from: https://www.dovepress.com/impact-of-endometriosis-on-life-course-potential-a-narrative-review-peer-reviewed-fulltext-article-IJGM

[12] Zondervan KT, Becker CM, Missmer SA. Endometriosis. N Engl J Med [Internet]. 2020 [cited 2024 May 31];382(13):1244–56. Available from: https://pubmed.ncbi.nlm.nih.gov/32212520/

[13] Monnin N, Fattet AJ, Koscinski I. Endometriosis: Update of Pathophysiology, (Epi) Genetic and Environmental Involvement. Biomedicines. 2023 Mar 22;11(3):978.

[14] Wang P-H, Yang S-T, Chang W-H, Liu C-H, Lee F-K, Lee W-L. Endometriosis: Part I. basic concept. Taiwan J Obstet Gynecol [Internet]. 2022 [citado el 31 de mayo de 2024];61(6):927–34. Available from: https://pubmed.ncbi.nlm.nih.gov/36427994

[15] Arab A, Karimi E, Vingrys K, Kelishadi MR, Mehrabani S, Askari G. Food groups and nutrients consumption and risk of endometriosis: a systematic review and meta-analysis of observational studies. Nutr J [Internet]. 2022 [citado el 31 de mayo de 2024];21(1). Available from: https://pubmed.ncbi.nlm.nih.gov/36138433/

[16] Geng R, Huang X, Li L, Guo X, Wang Q, Zheng Y, et al. Gene expression analysis in endometriosis: Immunopathology insights, transcription factors and therapeutic targets. Front Immunol [Internet]. 2022 [citado el 31 de mayo de 2024];13. Available from: https://pubmed.ncbi.nlm.nih.gov/36532015/

[17] Lazim N, Elias MH, Sutaji Z, Abdul Karim AK, Abu MA, Ugusman A, et al. Expression of HOXA10 gene in women with endometriosis: A systematic review. Int J Mol Sci [Internet]. 2023 [citado el 31 de mayo de 2024];24(16):12869. Available from: https://pubmed.ncbi.nlm.nih.gov/37629050/

[18] Zervou M, Papageorgiou L, Vlachakis D, Spandidos D, Eliopoulos E, Goulielmos G. Genetic factors involved in the co-occurrence of endometriosis with ankylosing spondylitis (Review). Mol Med Rep [Internet]. 2023 [citado el 31 de mayo de 2024];27(5). Available from: https://pubmed.ncbi.nlm.nih.gov/36960867/

[19] Abramiuk M, Mertowska P, Karolina Frankowska, Świechowska-Starek P, Małgorzata Satora, Polak G, et al. How Can Selected Dietary Ingredients Influence the Development and Progression of Endometriosis? Nutrients. 2024 Jan 2;16(1):154–4.

[20] Jung Yong Ahn, Yoon MJ, Hong ST, Cha H, Lee D, Hwa Seon Koo, et al. Three-dimensional microengineered vascularised endometrium-on-a-chip. Human Reproduction [Internet]. 2021 Aug 7;36(10):2720–31. Available from: https://academic.oup.com/humrep/article/36/10/2720/6345297

[21] Cousins FL, McKinnon B, Mortlock S, Fitzgerald HC, Zhang C, Montgomery GW, et al. New concepts on the etiology of endometriosis. The Journal of Obstetrics and Gynaecology Research. 2023 Feb 6;49(4):1090–105.

[22] Zhang Z, Ruan L, Lu M, Yao X. Analysis of key candidate genes and pathways of endometriosis pathophysiology by a genomics-bioinformatics approach. Gynecol Endocrinol [Internet]. 2019;35(7):576–81. Available from: http://dx.doi.org/10.1080/09513590.2019.1576609